N,N′-(1S)-[1,1′-Binaphthalene]-2,2′-diylbis-(2S,2′S)-pyrrolidine-2-carboxamide

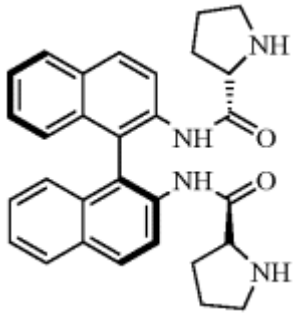
Gabriela Guillena, University de Alicante, Alicante, Spain
Carmen Nájera, University de Alicante, Alicante, Spain

Encyclopedia of Reagents for Organic Synthesis

DOI: 10.1002/047084289X.rn01044
Article Online Posting Date: September 15, 2009

Previous

Abstract



[891496-34-7] $C_{30}H_{30}N_4O_2$ (MW 478.24)

InChI = 1/C30H30N4O2/c35-29(25-11-5-17-31-25)33-23-15-13-19-7-1-3-9-21(19)27(23)28-22-10-4-2-8-20(22)14-16-24(28)34-30(36)26-12-6-18-32-26/h1-4,7-10,13-16,25-26,31-32H,5-6,11-12,17-18H2,(H,33,35)(H,34,36)/f/h33-34H

InChIKey = FYTHJMKJVUTERE-UBXIPSODCL

(used as a catalyst and as a ligand in enantioselective synthesis of aldol products and cyanosilylation of kentones, respectively)

Alternate Names: (S_a)-2,2′-bis[((2*S*)-pyrrolidin-2-ylcarbonyl)amino]-1,1′-binaphthalene, (*S*)-Binam-l-Pro.

Physical Data: mp 230 °C; $[\alpha]_{26}^{D} = -108.6°$ (*c* = 1, MeOH).

Solubility: soluble in most polar organic solvents; insoluble in hexane, ether, and

water.

Form Supplied in: not commercially available. Prepared from (S_a)-2,2′-diamino-1,1′-binaphthalene and protected L-proline, both commercially available.

Analysis of Reagent Purity: elemental analysis, NMR, HRMS, and X-ray structure.

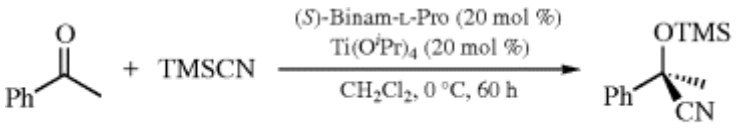
Preparative Methods: the reagent can be prepared by coupling (S_a)-2,2′-diamino-1,1′-binaphthalene with the mixed anhydride obtained from L-Boc-proline and isobutyl or ethyl chloroformate or by direct coupling of Boc-L-proline with (S_a)-2,2′-diamino-1,1′-binaphthalene (Binam) mediated by 1-ethyl-3-(3-methylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) or *N,N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP). The coupled intermediate was deprotected by using TFA. Alternatively, the reagent can be prepared by coupling (S_a)-2,2′-diamino-1,1′-binaphthalene with the acyl chloride derived from Fmoc-L-proline, and deprotection with piperidine.

Purification: by column chromatography and/or recrystallization from CH_2Cl_2/hexane or $CHCl_3$/ether.

Handling, Storage, and Precaution: the reagent is stable for months when stored in air at room temperature.

Enantioselective Cyanosilylation of Ketones

The generation of chiral quaternary stereocenters is a challenging task, with the addition of trimethylsilyl cyanide (TMSCN) to ketones being one of the most successful examples.[1] (*S*)-Binam-L-Pro was used as a ligand for the enantioselective addition of TMSCN to acetophenone (eq 1). The catalytic complex obtained by reaction with titanium fetra isopropoxide gave the O-TMS cyanohydrin with 47% yield and 33% ee. Better results (up to 90% yield and 94% ee) were obtained under similar reaction conditions using the bisamide derived from 1,2-diphenylethane-1,2-diamine and proline.[2]

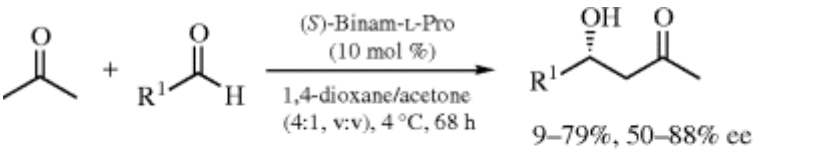


(1)

Enantioselective Direct Aldol Reaction

The use of organocatalytic methods[3] for the enantioselective direct aldol reaction[4]

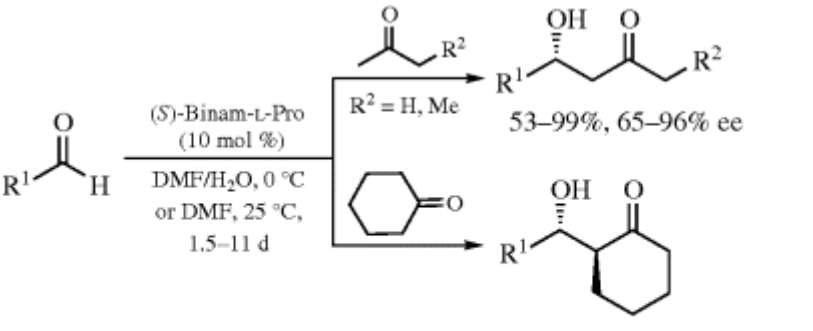
has reached its maturity allowing the synthesis of chiral molecules with high atom efficiency.[5] (*S*)-Binam-L-Pro was first used as an organocatalyst in the intermolecular direct aldol reaction of aromatic aldehydes and alkyl or cyclic ketones using two different protocols.[6] Whereas in one protocol the mixture of 1,4-dioxane/ketone (4:1) at 4 °C were the best reaction conditions, giving the corresponding aldols with 9–79% yield and 50–88% ee's (eq 2),[6a] DMF/water (1:1) at 0 °C or DMF at 25 °C afforded better results in the second instance (52–99% yield, 78–95% ee).[6b] Under the latter reaction conditions, the use of L-proline as catalyst afforded the racemic product.



(2)

$R^1 = C_6F_5$, 4-CNC_6H_4, 4-$CF_3C_6H_4$, 2,6-$Cl_2C_6H_3$, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, Ph, β-naphthyl

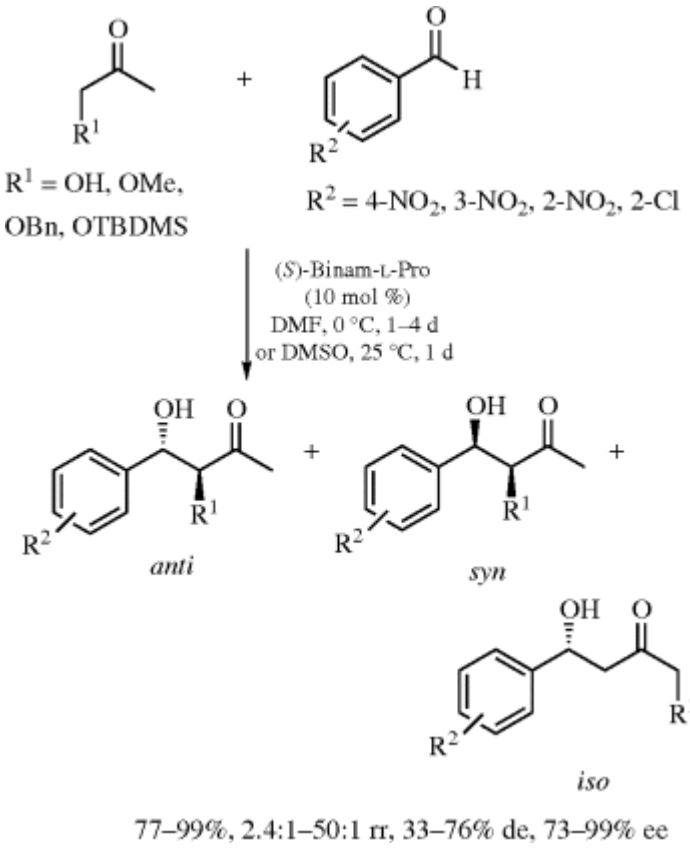
When 2-butanone was used as precursor, the reaction took place nearly exclusively at the methyl position, to give the *iso*-isomer preferentially (eq 3). These conditions permitted the recovery by acidic–basic extraction and reuse of catalyst without any detrimental effect on the obtained yields and enantioselectivities during three additional cycles.[6b] Alternatively, $CHCl_3$/ketone (1:1) at –27 °C gave the corresponding aldols with 35–98% yield and 68–95% ee.[7]



(3)

$R^1 = 4\text{-}NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-$ClC_6H_4$, Ph, C_6H_{11}, $(CH_3)_2CH$

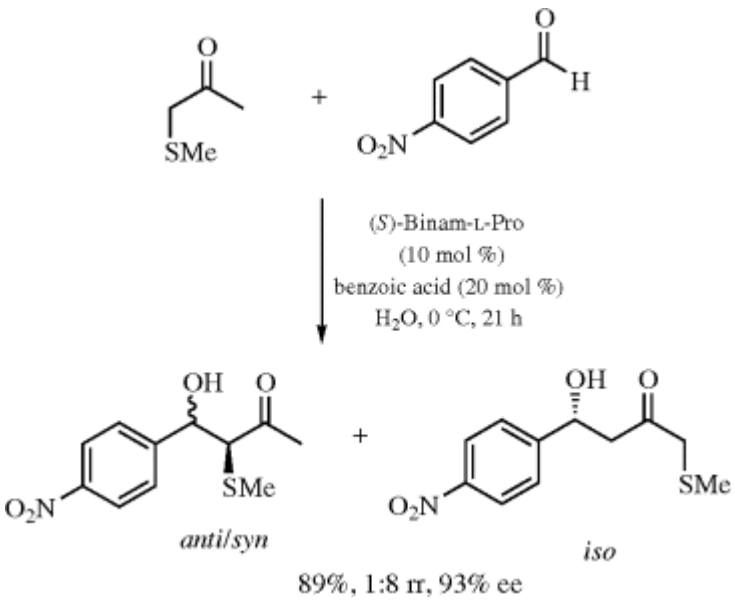
Under similar conditions, (*S*)-Binam-L-Pro was used as catalyst in the reaction between *a*-alkoxy ketones (R^1 = OH, OMe, OBn, OTBDMS) and aromatic aldehydes (eq 4) to give mainly the *anti*/*syn*-regioisomer mixture, with small amounts of corresponding *iso*-regioisomer being formed. The diastereoselectivity was dependent on the nature of R^1 group, with the *anti*-regioisomer obtained as the main product. The enantioselectivity of the process ranged from 73 to 99%. For the case of *a*-hydroxyacetone (R^1= OH), the best conditions employed DMSO at 25 °C, affording mainly the *anti*-isomer with 85% ee. These results are comparable in terms of regio- and diastereoselectivities to those obtained with L-proline, with the advantage that (*S*)-Binam-L-Pro prolinamide could be recovered when DMF was used as solvent.[8]



(4)

The reaction rate was highly increased by the addition of catalytic amounts of carboxylic acids, with benzoic acid giving the best results. For instance, using 20 mol % benzoic acid in the reaction between acyclic and cyclic alkyl ketones with 4-nitrobenzaldehyde in DMF:H_2O, the reaction time was reduced from 3 d to only 1.5 h, maintaining the enantioselectivity. This procedure enabled reactions at –20 °C with enhanced enantioselectivity (86–99%). Using benzoic acid as cocatalyst allowed the reaction to be conducted in water without addition of DMF.[9] The combination of (*S*)-Binam-L-Pro (10 mol %) and benzoic acid (20 mol %) in either DMF or pure water permitted the use of less reactive ketones such as *a*-(methylsulfanyl)acetone,

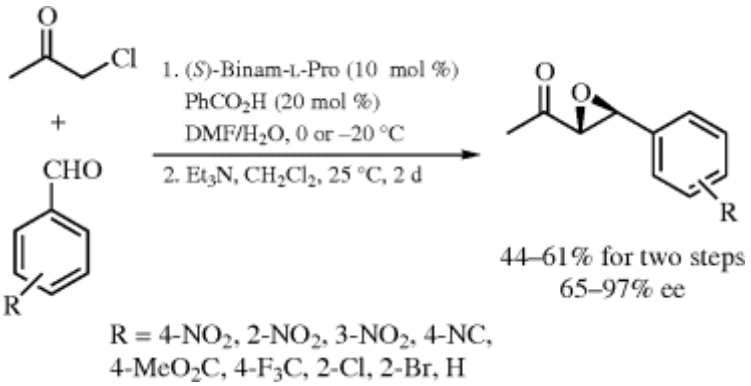
giving mainly the *iso*-isomer with an excellent 93% ee (eq 5).[10] *a*-Alkoxy ketones give similar yields, regio-, diastereo-, and enantioselectivities to those achieved in the absence of acid, but in shorter reaction times (3–24 h).



(5)

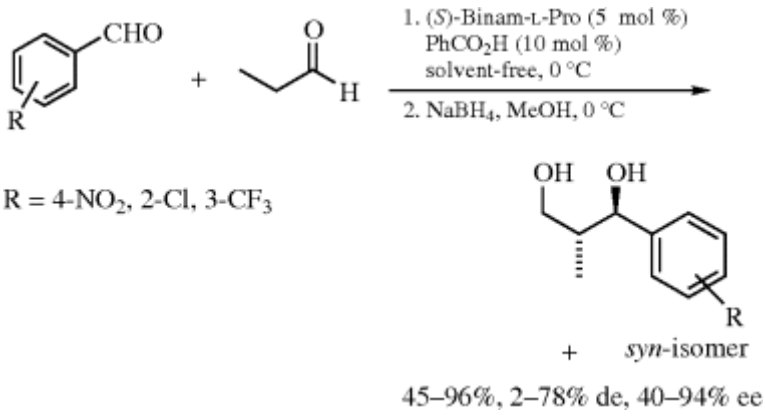
Other carboxylic acids can be used as cocatalyst. For instance, using acetic acid (10 mol %) as cocatalyst in toluene at –40 °C, the aldol products were obtained in 45–91% yield, 40–96% de, and 67–95% ee but longer reaction times being required (2–3 d).[11] Using a micellar agent stearic acid (20 mol %) as cocatalyst in water at 2 °C permitted reduction of the amount of nucleophilic ketone to 3 equiv, providing 61–99% yield and 58–93% ee in only 12 h.[12]

Using benzoic acid as cocatalyst, *a*-chloroacetone mainly produces the *anti*-isomer in moderate yields, but high diastereo- and enantioselectivities. These aldol products were easily converted into chiral (3*R*,4*S*)-*trans*-epoxides by treatment with triethylamine (eq 6).[13]



(6)

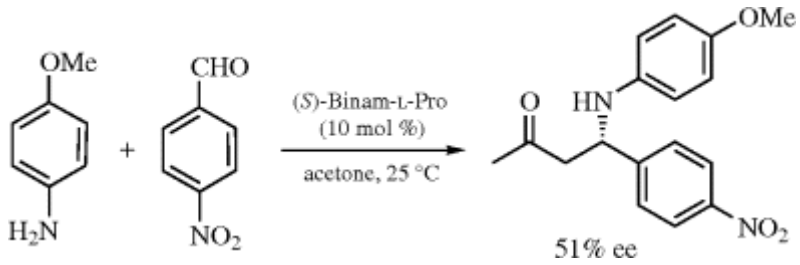
A further improvement involved the use of solvent-free conditions. Thus, mixing the reagents by simple magnetic stirring allowed reduction of nucleophile to only 2 equiv, catalyst loading of 5 mol %, and in some cases reduced reaction time. The aldol reaction between cycloalkyl, alkyl, and *a*-functionalized ketones with aldehydes gave the expected aldol products with similar yields, regio-, diastereo-, and enantioselectivities to those obtained in solution. Furthermore, aldehydes can also be used as nucleophiles providing, after in situ reduction of the aldol products, chiral 1,3-diols with moderate to good enantioselectivities mainly as *anti*-isomers (eq 7).[14]



(7)

Enantioselective Mannich Addition

A single example of the use of (*S*)-Binam-L-Pro (10 mol %) as catalyst for this type of transformation has been reported.[7] Thus, the multicomponent[15] Mannich reaction between 4-nitrobenzaldehyde, 4-methoxyaniline, and acetone afforded the corresponding *b*-amino ketone with 51% ee at 25 °C (eq 8).



(8)

Bibliography

1. (a) Ramón, D. J.; Yus, M., Curr. Org. Chem., 2004, **8**, 149. Links (b) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J.; Baro, A., Eds.; Wiley-VCH Verlag: Weinheim, 2005. (c) Ramón, D. J.; Yus, M., Chem. Rev. 2006, **106**, 2126. Links

2. Xiong, Y.; Huang, X.; Gou, S.; Huang, J.; Wen, Y.; Feng, X., Adv. Synth. Catal. 2006, **348**, 538. Links

3. (a) Berkessel, A.; Gröger, H., *Asymmetric Organocatalysis: From Biomimetic Concepts to Application in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (b) *Enantioselective Organocatalysis*; Dalko, P. I. Ed.; Wiley-VCH: Weinheim, 2007. (c) Guillena, G.; Ramón, D. J., Tetrahedron: Asymmetry 2006, **17**, 1465. Links (d) Guillena, G.; Ramón, D. J.; Yus, M., Tetrahedron: Asymmetry 2007, **18**, 693. Links

4. Guillena, G.; Nájera, C.; Ramón, D. J., Tetrahedron: Asymmetry 2007, **18**, 2249. Links

5. (a) Trost, B. M., Science 1991, **254**, 1471. Links (b) Sheldon, R. A., Pure Appl. Chem. 2000, **72**, 1233. Links (c) Trost, B. M., Acc. Chem. Res. 2002, **35**, 695. Links (d) Trost, B. M.; Frederiksen, M. U.; Mathias, U.; Rudd, M. T., Angew. Chem., Int. Ed. 2005, **44**, 6630. Links (e) Guillena, G.; Ramón, D. J.; Yus, M., Angew. Chem., Int. Ed. 2007, **47**, 2358. Links

6. (a) Gryko, D.; Kowalczyk, B.; Zawadzki, L., Synlett 2006, 1059. Links (b) Guillena, G.; Hita, M. C.; Nájera, C., Tetrahedron: Asymmetry 2006, **17**, 729. Links

7. Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A., Tetrahedron: Asymmetry 2006, **17**, 2754. Links

8. Guillena, G.; Hita, M. C.; Nájera, C., Tetrahedron: Asymmetry 2006, **17**, 1027. Links (Corrigendum: Tetrahedron: Asymmetry 2007, **18**, 1030). Links

9. Guillena, G.; Hita, M. C.; Nájera, C., Tetrahedron: Asymmetry 2006, **17**, 1493.

Links (Corrigendum: Tetrahedron: Asymmetry 2007, **18**, 1031). Links

10. Guillena, G.; Hita, MC.; Nájera, C.; ARKIVOC 2007, **iv**, 260. Links (Corrigendum: ARKIVOC 2007, **i**, 146). Links
11. Ma, G. N.; Zhang, Y. P.; Shi, M., Synthesis 2007, 197. Links
12. Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G., Org. Lett. 2007, **9**, 1247. Links
13. Guillena, G.; Hita, M. C.; Nájera, C.; Tetrahedron: Asymmetry 2007, **18**, 1272. Links
14. (a) Guillena, G.; Hita, M. C.; Nájera, C.; Viózquez, S. F., Tetrahedron: Asymmetry 2007, **18**, 2300. Links (b) Guillena, G.; Hita, M. C.; Nájera, C.; Viózquez, S. F., J. Org. Chem. 2008, **73**, 5933. Links
15. Ramón, D. J.; Yus, M., Angew. Chem., Int. Ed. 2005, **44**, 1602. Links